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FULL-LENGTH ORIGINAL RESEARCH

Clinical course and variability of non-Rasmussen, nonstroke motor and sensory epilepsia partialis continua: A European survey and analysis of 65 cases

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Summary

Purpose: To gain new insights into the clinical presentation, causes, treatment and prognosis of epilepsia partialis continua (EPC), and to develop hypotheses to be tested in a prospective investigation.

Methods: In this retrospective multicenter study, all cases were included that fulfilled these criteria: constantly repeated fragments of epileptic seizures, with preserved consciousness, lasting ≥1 h and representing locally restricted motor or sensory epileptic activity. Single episodes were included when they lasted for a minimum of 1 day. EPC with Rasmussen syndrome and acute stroke were excluded.

Key Findings: Three time courses with two subtypes each were distinguished, that is, EPC as a solitary event (de novo or in preexistent epilepsy); chronic repetitive nonprogressive EPC (with frequent or rare episodes); and chronic persistent nonprogressive EPC (primarily or evolving out of an episodic course). These were unrelated to etiologies (morphologic lesions 34%, inflammatory 29%, systemic disorders 9%, idiopathic 5%, unknown 23%). Precipitation and inhibition of seizures is a frequent feature of EPC. Levetiracetam and topiramate have improved the possibilities for pharmacotherapy. Topiramate seems to be particularly effective with dysontogenetic etiologies.

Significance: The existence of several clearly distinct courses of nonprogressive EPC is a new finding. These distinctions will be further investigated in a prospective study with precise protocols for electroencephalography (EEG), imaging, and other studies. This should better establish the relation of motor and somatosensory EPC; further clarify the relations, pathogenesis, and significance of the different types and their etiologies; and possibly identify more semiologic variants. It should also provide more precise knowledge about therapy and modification of ictogenesis by external stimuli.

KEY WORDS: Epilepsia partialis continua etiologies, Nonprogressive epilepsia partialis continua, Sensory epilepsia partialis continua, Focal status epilepticus, Aura continua, Developments of epilepsia partialis continua.

Epilepsia partialis continua (EPC) was first described, and the term proposed by Aleksei Yakovlevich Kozhevnikov (1836–1902), in a report on "a special form of cortical epilepsy" to the Russian Society for Neuropathology and Psychiatry on January 21, 1894 (Kozhevnikov, 1895). He

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described four cases of uninterrupted local cloni and proposed to call the condition ''epilepsia partialis continua.'' In the discussion Dr. Minor reported similar observations, the symptoms in one case being sensory for which he suggested the term ''aura continua.'' When Kozhevnikov disagreed, Dr. Filatov proposed as a compromise to call the condition ''Kozhevnikov's epilepsy.'' Interestingly, all three terms came and still are in use.

EPC has been described in a great variety of clinical contexts and etiologies (Wieser & Chauvel, 2008). Among these, the chronic-progressive inflammatory Rasmussen syndrome (Dubeau et al., 2008) is today considered an own nosologic entity and will not be discussed here. Another well-known relation is to the acute phase of stroke (Sinha & Satishchandra, 2007).

Beyond two old (Thomas et al., 1977; Cockerell et al., 1996) and two more recent (Gurer et al., 2001; Sinha & Satishchandra, 2007) reviews of larger case series, little effort has been taken to further investigate and map EPC. In particular, knowledge is insufficient about variations in the presentation, course, and development of EPC, and relations to other seizure types, causative factors, syndromatic aspects, and response to therapy.

Following the London Status Epilepticus Symposium of 2007 (Shorvon et al., 2007), an informal study group of European centers was formed to address these questions. Twenty-one cases from nine centers were collected and presented at the 2nd European Status Epilepticus Symposium (Wolf et al., 2009). In response, 10 additional centers joined the study group, and recruitment was extended until September 30, 2009, where 65 cases were enrolled. These are presented here. The aims of this study are to get new insights into the clinical presentation, causes, treatment, and prognosis of EPC, and to develop hypotheses to be tested in a prospective investigation.

Material and Methods

In this retrospective multicenter study, no attempts were made to systematize the case collection. All cases were included that fulfilled the definition below and had no indication of having Rasmussen encephalitis or being acute symptoms of stroke, both conditions appearing to be sufficiently described already. Some participating groups had internally registered EPC cases in view of possible publication; others had not. Both neurologic and pediatric groups participated.

Definitions

There is at present no generally accepted definition of EPC. Thomas et al. (1977) proposed one hour as the minimum duration of a condition to be accepted as EPC, with regular or irregular muscular twitches affecting a limited part of the body and recurring at intervals not above 10 s. Maximum intervals, however, are not generally included in the definition (Obeso et al., 1985; Cockerell et al., 1996), and a shorter minimum duration (30 min) was proposed by Wieser and Chauvel (2008). These definitions apply to motor EPC, to which many authors restrict the term, not discussing, however, where to draw the line to somatosensory symptoms that often occur together with motor signs or as an isolated symptomatology (Penfield & Jasper, 1954; Janz, 1969). If somatosensory aura continua is included, should not other types of aura continua also be considered, for example, visual (Palem et al., 1970; Wolf, 1980), auditory (Wolf, 1983), gustatory (Wieser et al., 1985; Seshia & McLachlan, 2005), and olfactory (Wolf, 1982; Manford & Shorvon, 1992), distortion of proprioception (Scott & Masland, 1953), epigastric and autonomic (Scott & Masland, 1953; Wolf, 1980), dysmnesic (Wolf, 1980), and anxiety (Scott & Masland, 1953; Henriksen, 1973)? In some of these, the distinction from nonconvulsive, complex partial status can be difficult as was discussed by Wieser and Fischer (2009) and Chicharro and Kanner (2009). Another case is aphasia or dysphasia caused by epileptic status activity (De Pasquet et al., 1976), where it is difficult to determine if it is an ictal or, rather, postictal symptom (Wieser & Chauvel, 2008).

Penfield & Jasper, (1954, p. 37) found it ''justifiable to extend the meaning of the term to cover any type of focal seizure which is continuous without spreading to a larger seizure or with only occasional spread.'' We agree.

For the purpose of this study we defined EPC [in distinction from simple focal status epilepticus (SE) with frequently recurring, but still distinguishable separate seizures] as a condition of continuously repeated fragments of epileptic seizures (motor or sensory), with preserved consciousness, lasting ≥1 h, and representing locally restricted epileptic activity. Our inclusion criteria were pragmatic: we included cases with focal motor or sensory symptoms, and excluded less clearly delineated conditions, that is, psychic, autonomic, and cognitive types of aura continua, and dysphasic SE. Single episodes were included when they lasted for a minimum of 1 day.

Results

For a patient overview see Table 1. Three types of development could be distinguished in our cohort, that is:

1. EPC as a solitary event
2. Chronic repetitive nonprogressive EPC
3. Chronic persistent nonprogressive EPC

EPC was rated as persistent when in the reported period it was present daily, whereas shorter interruptions, for example during sleep, were accepted.

Type 1 was reported in 12 cases of different etiology and pathogenesis, both de novo (n = 7), and in established epilepsy (n = 5, Table 2). The episodes lasted from 4 days to 3 months, except for one patient with EPC due to probable herpes simplex encephalitis who died after 36 h.

Table 1. Patient overview

	All N = 65	Type 1 Single episode N = 12	Type 2 Episodic recurrent EPC N = 18	Type 3 Persistent EPC N = 35
Age in years (mean ± SD)	2–70 (27.4 ± 19.5)	2–66 (27.2 ± 24.3)	6–70 (31.8 ± 21.7)	6–63 (25.2 ± 16.5)
Sex: men/women	37/28	6/6	8/10	23/12
Duration of EPC (mean years ± SD)	6.5 ± 6.5	36 h–3 months	8.4 ± 9.2	6.2 ± 4.8
Age at onset of epilepsy (mean ± SD)	5 month–68 year (16.8 ± 18.9)	5 month–66 year (21.6 ± 26.8)	9 month–68 year (18.3 ± 19.6)	6 month–60 year (14.4 ± 15.2)
Age at onset of EPC (mean ± SD)	6 month–69 year (22.3 ± 20.0)	1–66 year (27.4 ± 26.8)	2–69 year (22.7 ± 21.0)	4–60 year (20.0 ± 16.5)
Interval from onset epilepsy to EPC (mean ± SD)	−2–28 year (4.3 ± 6.8)	0–22 year (6 ± 7.9)	0–15 year (3.2 ± 5.3)	−2–28 year (4.1 ± 7.1)
Etiologies				
Morphologic lesions				
FCD	9 (13.8%)	1	3	5
Tumor incl. DNT	4 (6.2%)	1	1	2
AVM, cavernoma	2 (3.1%	0	0	2
Postoperative/trauma	2 (3.1%)	0	0	2
Subdural hematoma	1 (1.5%)	0	1	0
Unspecified lesion	3 (4.6%)	0	1	2
Vascular lacunae	1 (1.5%)	0	0	1
Inflammatory				
Tick-borne encephalitis	9 (13.8%)	0	0	9
Herpes simplex encephalitis	1 (1.5%)	1	0	0
Nonspecific	7 (10.8%)	1	3[a]	3
Creutzfeldt-Jacob disease	2 (3.1%)	2	0	0
Systemic				
Morbus Alpers	5 (7.7%)	0	1	4
MELAS	1 (1.5%)	0	0	1
Idiopathic				
BECTS	3 (4.6%)	1	2	0
Unknown	15 (23.1%)	5	6	4

[a]One of these, a 41-year-old woman with frequently repeated episodes of motor EPC starting at age 28 and on brain biopsy diagnosed as atypical Rasmussen encephalitis has meantime been histologically rerated as Rasmussen encephalitis, adult form.

Table 2. Single episodes of EPC with etiologies or pathogenesis (type 1, n = 12)

1. In preexisting epilepsies
   a. Sleep deprivation, stress in cryptogenic focal epilepsy
   b. Anterior opercular syndrome, CSWS in idiopathic rolandic epilepsy
   c. Encephalitis (suspected *herpes simplex*) in cryptogenic focal epilepsy
   d. Epilepsy with focal cortical dysplasia, reduction of valproate, and oxcarbazepine after seizure control
   e. Side effect of zonisamide treatment of resistant multifocal epilepsy
2. De novo
   a. Local encephalitis after biopsy of oligodendroglioma
   b. HHE syndrome, initial phase of hemiconvulsions
   c. Systemic infectious disease
   d. Creutzfeldt-Jacob disease (2)
   e. Unclarified (2)

Type 2 was found in 18 cases. This pattern persisted until inclusion, having been present for up to 29 years. This type seems not to be homogeneous but to split into two subgroups. In the first (2a, ''frequent,'' n = 10), the single episodes of EPC lasted not longer than 24 h and occurred more than once per month. In the other subgroup (2b, ''rare,'' n = 8) the single episodes lasted several days up to some weeks and occurred at longer intervals of typically several months. Within one episode of type 2b, the EPC could be fully continuous or present with brief interruptions. Both patterns remained stable over periods up to 29 (2a) and 25 years (2b), respectively.

Type 3 was described in 35 cases, lasting from 1–25 years. In seven of these, EPC started with episodes (three type 2a and four type 2b) and after 3 months to 4 years secondarily evolved into the persistent type. The reverse course was seen only once—not as a spontaneous evolution but as a partial effect to therapy with tiapride.

EPC was rarely the only manifestation of epilepsy (8 of 65). The concomitant seizure types were simple focal in 45 cases, secondarily generalized tonic–clonic in 30, and complex partial in 15. The values add up to >65, since many patients had more than one, and one had multiple seizure types. Three had a history of convulsive status epilepticus,

and one was in addition to epilepsy diagnosed with psychogenic nonepileptic seizures. When the habitual seizures had a clear focal onset, the semiology of the EPC could always be recognized as a seizure fragment. This was not possible in cases where EPC was the only clinical manifestation, when the patient had generalized tonic–clonic seizures without clinical focal onset, and in the case of systemic diseases and multiple seizure types.

The majority of patients (49 of 65) had the motor type of EPC, and in seven the symptoms were reported as sensorimotor. Five patients had somatosensory EPC and four had visual EPC.

Clinical presentation

In motor and sensorimotor EPC, the symptoms were restricted to a narrow localization, sometimes just one muscle, in 18 cases, and involved a whole limb in 7. In 24, the distribution was unilateral, although more expanded, involving more than one limb. In 10 patients (seven bilateral) there were indications of more than one focus producing EPC.

The local distribution is shown in Table 3. Face and upper extremity are predominantly affected.

Findings

Neurologic findings (Table 4) are present in most cases, demonstrating that EPC predominantly is a symptom of brain pathologies that go beyond mere dysfunction. However, at least in five patients the deficits were transient (Todd paresis), and in cases of type 3 with very frequent motor symptoms it can be impossible to distinguish irreversible damage from a permanent postictal state—unless a successful treatment is eventually found and the symptoms remain or resolve. Twenty patients (30.8%) had no neurologic deficit, indicating that EPC may also be the sign of a merely functional disturbance.

EEG

EEG investigations, usually repetitive, were a consistent part of the diagnostic work-up in all cases but did not follow a uniform protocol. We tried to distinguish between interictal EEG, ictal EEG of individual seizures (if applicable), and ictal EEG during EPC but in retrospect this was often not possible. Interictal EEGs always exists, but ictal recordings of seizures or of EPC were not always obtained. When the information from interictal state, single seizures, and EPC is summarized, including only the most specific finding of each patient, epileptiform activity was found in 42 cases (64.6% of all cases, 8 in type 1, 13 in type 2, and 21 in type 3), slow waves in 11 cases (two each in types 1 and 2, and seven in type 3), and local flattening in one case of type 3. The EEG was unrevealing in only 11 patients (two of type 1, three of type 2, six of type 3).

Table 3. Local distribution of EPC (without visual EPC, n = 61)

Face	15
Face and arm	16
Arm/hand	11
Arm and leg	2
Leg/foot	7
Hemibody	6
2 Loci	4

Table 4. Neurologic findings

Mild hemiparesis	7
Hemiparesis	13
Monoparesis foot	2
Hemiparesis and -anopia	1
Monoparesis hand	4
Anterior opercular syndrome and aphasia/dysphasia	2
Facial paresis	2
Hemiparesis and ataxia	1
Hemiparesis and aphasia	3
Hemiparesis and sopor	1
Blindness, learning disabilities	1
Ataxia	2
Mild mental retardation	1
Rapid deterioration	3
Todd's paresis	5
Speech arrest	1
Visual field defect	2
None	20

Imaging

The etiologies as presented in Table 1 are based upon a multitude of different modalities and protocols of various imaging methods that were applied in 62 patients (95.4%). Some of these were very advanced, others of less reliable expertise. Various focal abnormalities (see Table 1) were found in 50 cases (80.6%) and all of them corresponded to seizure semiology. In 37 cases (56.9%) only magnetic resonance imaging (MRI) was performed, with positive findings in 30. Ten patients (15.4%) were investigated by computed tomography (CT) and MRI with positive findings in six of which in four only MRI showed pathology. CT scan only was applied in three patients with positive findings in two. MRI and single photon emission computed tomography (SPECT) were performed in three cases and pathology was found in all three (in two only in SPECT); CT, MRI, and SPECT were performed in three cases, two of which had positive findings only with SPECT. In one patient, only SPECT was applied with a positive result. In three patients, pathology was revealed only when more methods were combined [CT + MRI + angiography; MRI + positron emission tomography (PET); MRI + SPECT + PET (published by Siclari et al., 2009) in one each]. In three patients, all with tick-borne encephalitis, no imaging investigations were done because they were seen in a far-Eastern rural areas of Russia where these methods were not available.

Etiology and pathogenesis

The etiologies (see Table 1) could be clarified in 50 cases (76.9%). Local morphologic lesions were demonstrated in 21, and one 63-year-old patient had multiple vascular lacunae. Nineteen patients had inflammatory etiologies including nine cases of tick-borne encephalitis. Six patients had systemic disorders (five with morbus Alpers including a sibship of two, and one with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes [MELAS]). Three patients had idiopathic rolandic epilepsy of childhood, which in two was complicated by continuous spikes and waves during slow sleep (CSWS) and anterior opercular syndrome, whereas in the third (followed until age 18) intermittent episodes of EPC with numbness in the tip of tongue, right angle of mouth, and fingertips accompanied by epileptiform EEG activity were the only unusual feature in an otherwise perfectly benign course, the patient being totally seizure free and without drugs since age 12.

The pathogenesis was apparent in most type 1 cases (Table 2) but less often in the other types. Of the 18 type 2 cases, the pathogenesis of the first or several episodes could be defined in 5 and was different in each [intracranial hematoma; tumor resection; period of increased seizure activity; prolonged aura of secondary generalized tonic–clonic seizures (GTCS); presenting symptom of unknown etiology]. In all others the development of EPC seemed for reasons not clearly identified to be part of the evolution of the epilepsy. Of the 35 chronic persistent cases, EPC was the presenting symptom in 10, and caused by antiepileptic drug (AED) withdrawal in one. In nine cases the etiology was tick-borne encephalitis, where EPC in eight started with an interval of 4 weeks to 2.5 years after the acute meningoencephalitis, and in one case, 3 months after a tick bite without an acute inflammatory phase.

Therapy

EPC is known as a condition that is difficult to treat. Like other status types, it could often be interrupted by benzodiazepines. To reach sustained effect, a multitude of AEDs were applied, often without success. Treatments that were found to stop or at least alleviate EPC usually did it only in individual cases (Table 5). Apart from several cases where benzodiazepines temporarily interrupted the EPC, two AEDs presented a better success rate. Topiramate was effective in 7 of 28 cases where it was tried, and patients with a dysontogenetic etiology of EPC (four cortical dysplasias and one arteriovenous malformation) seemed to respond best. Levetiracetam was given to 26 patients and was successful in 8. These included five patients with inflammatory etiologies (three with tick-borne encephalitis; one with oligodendroglioma and perineoplastic inflammation; and one with chronic local encephalitis, which is now considered an atypical adult-onset case of Rasmussen encephalitis). In six cases of different etiologies, treatment with steroids was successful, in two of these, however, given in combination with clonazepam. Successful treatment of EPC not necessarily was also effective against the patient's individual seizures.

Precipitation and inhibition of ictal activity

In 24 of our patients (36.9%) trigger mechanisms were observed either for precipitation of individual seizures (5) or for increase of EPC (19). This feature was found in 16 of 49 with motor, 4 of 7 with sensorimotor, 3 of 5 with somatosensory, and 1 of 4 with visual EPC. The trigger mechanisms were motor action in 12, touch in 9, passive movement in 2, and intention to move, ''mental exercise,'' light and noise in one each (more than one trigger was present in two cases; exposure to light was a trigger of visual seizures in a patient who developed visual EPC). Modulation of EPC intensity by motor or sensory input was described in seven of the nine cases with motor EPC due to tick-borne encephalitis, and in the same cases it was reported that physical and emotional rest reduced EPC. More specific external inhibition of EPC was reported in four cases, one each by relaxation, by passive immobilization of the convulsing limb, or to the contrary by its strong innervation; touching a trigger zone in one patient could either inhibit the development of sensory EPC or precipitate a tonic seizure, depending on the timing of the stimulus. One patient reported self-inhibition of spread of focal motor seizures by deep relaxation at seizure onset.

Discussion

In this study, three different time courses of EPC were represented: solitary event (type 1), chronic repetitive nonprogressive (type 2), and chronic persistent nonprogressive (type 3). Chronic progressive EPC, or Rasmussen syndrome, can be added as type 4 but was not part of this investigation as it is already well-described.

Type 1

This type is probably underrepresented in this survey due to ascertainment bias and because stroke, one important etiology, was excluded from the collection since it appeared already well-described. Two subgroups could be distinguished: 1a single episodes of EPC in preexisting epilepsies and 1b acute symptomatic EPC. Stroke is the best-known etiology in 1b but there are many others. Factors conditioning EPC in established epilepsies should be studied systematically and prospectively. The factors observed here include sleep deprivation and changes in antiepileptic drug treatment, that is, well-known facilitating factors of seizures and, in particular, status epilepticus. The question remains open, why in these cases they resulted in EPC. Notably, by far the most common accompanying seizure type in our patients was simple focal. This seems to indicate that strong inhibition of seizure spread is a general feature of the

Table 5. Successful treatments

EPC type	Successful treatment (N)	Successful medication (*-partial effect)	Etiology of EPC	Failed medications
Type I	1	TPM	Unknown	VPA, LEV, PHT, MDZ, PB
(single period)	1	TPM + OXC*	FCD	VPA, CZP, LTG, OXC, LEV, TPM
	1	VPA + OXC*	FCD	–
	1	LEV	Tumour	–
	2	NZP*	Unknown	VPA, BZD, VGB, LTG
	1	CZP + steroids	Idiopathic	VPA, LEV, CZP
	1	PGB	Unknown	LEV, PHT, CZP
Type 2	1	TPM	FCD	CBZ, CLB, CZP, PHT, LTG, MZD, PGB, PRM, TPM
(episodic recurrence)	1	LEV	FCD	LZP, DZP, CZP, PHT, VPA, TPM, PB, CBZ, Thiopental
	1	LEV*	FCD	TPM, LTG, STM, OXC, CBZ, VPA
	1	OXC*	Unspecified lesion	CBZ, VPA
	1	VNS*	Unknown	All
	1	CBZ + VPA	FCD	–
	1	VNS (50%), LEV, BZD*	Nonspecific encephalitis	CBZ, VPA, PGB, LTG
	1	LEV*	Tumor	LTG, CBZ, CLB, VPA, PHT, LZM
	1	Steroids + CZP*	Idiopathic	VPA, LEV, OXC
	1	Steroids	Unknown	VPA, VGB, CBZ, PB, TPM, LTG, CLB, NZP, CZP
	1	VPA*	Nonspecific encephalitis	PB, OXC, LEV
	1	LTG	Traumatic	LTG, VPA, PHT, CBZ, LEV
Type 3	2	TPM	FCD	CBZ, CLB, CZP, PHT, GBP, LTG, MDZ, OXC, PB, PRM, VPA, VGB
(persistent)	1	PB	Tumor	CBZ, VPA, TPM, LEV
	1	TPM	Postoperative	OXC, PGB, VPA, CBZ
	1	TPM	FCD	CBZ, CLB, CZP, PHT, LEV, LTG, PB, PRM, VPA, VGB
	1	CZP*	Postoperative	CBZ, PHT, VPA, PB, TPM, OXC, LTG, PHT
	1	CBZ + TPM	Unknown	VPA, PRM, PB, CBZ, CZP, LTG
	2	Steroids*	FCD	Several
	1	LTG + GBR + Tiapridex*	Encephalitis	CBZ, CZP, CLB, VPA, LEV, PHT, NZP, LZP
	1	Steroids + Plasmapheresis*	Nonspecif. encephalitis	CBZ, VGB, PHT, GBP, VPA, LTG, ESM, PRM, STM, LEV, OXC, TGB
	1	ESM + VGB*	Morbus Alpers	PHT, DZP, CZP, VPA, PB, THIOPENTAL, MDZ, OXC, BRV, LEV, VGB, CLB, ESM, prednisolone, lidocaine
	1	VGB*	FCD	CBZ, OXC, PHT, PB, VPA, LEV, TPM, GBP, LTG
	1	Surgery*	Cavernoma	CBZ, GBP, LTG, LEV, TPM, VPA
	1	LEV*	TBE	VPA, CBZ, LTG, CZP, DZP
	1	CZP*	TBE	CBZ
	1	VPA + PB*	TBE	CBZ, VPA
	1	VPA + LEV*	TBE	VPA, LTG, TPM
	1	LEV*	TBE	CBZ, CZP, DPH, prednisolone
	1	LTG + VGB*	MELAS	CBZ, VPA, PB, PHT, GBP, CLB

BRV, brivaracetam; BZD, benzodiazepines; CLB, clobazam; CZP, clonazepam; DZP, diazepam; ESM, ethosuccimide; LEV, levetiracetam; LTG, lamotrigine; LZM, lacozamide; LZP, lorazepam; MDZ, midazolam; NZP, nitrazepam; OXC, oxcarbazepine; PB, Phenobarbital; PGB, pregabalin; PHT, phenytoin; PRM, primidone; STM, sulthiam; TGB, tiagabin; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid.

ictogenesis in these patients, which may also be expressed in the manifestation of EPC.

A caveat about single episodes of EPC in a cross-sectional survey is that they could represent first episodes of type 2, especially if no clear etiology can be defined. To clarify this prognostic question will be one of the tasks for a prospective study.

Type 2

Again, two clearly separated subtypes appeared: 2a, with frequent brief episodes; and 2b, with rare long episodes. The two patterns did not overlap or alternate in any patient, and remained the same over periods of up to >20 years, indicating that they do not represent opposite ends of a continuum but separate pathogenic mechanisms. In subtype 2a EPC

looks like a type of seizure with unusually long duration, whereas subtype 2b could be related to periodic or episodic changes in seizure susceptibility. Interestingly, both subtypes could develop into type 3. An important task for the prospective study will be to confirm these subtypes and better understand their pathogenesis.

Type 3

There are again two subgroups: 3a, starting as type 2; and 3b, immediately persistent; but the subgroups do not look fundamentally different. It is not known at present if this difference has any particular significance. Type 3 was seen with all etiologies, whereas it was the only type connected with tick-borne encephalitis. Here it started with a delay of 4 weeks to 2.5 years (mean ≈10 months). Although the persisting type in seven cases evolved from recurrent episodes of EPC, it was in 8 of 35 cases already part of the presenting symptomatology. In one of three cases where the pathogenesis of EPC was related to changes in AED treatment (discontinuation of carbamazepine [CBZ] by patient), the EPC persisted and has now lasted 20 months.

Clinical presentation and diagnosis

The symptoms of EPC are likely to reflect epileptic activity restricted to the ictal-onset zone, and are categorically identical with the first signs and symptoms of the patients' individual seizures. However, this is not always easy to recognize, especially when the latter habitually are brief, unimpressive, or merely subjective. The continuous repetition of such seizure fragments can create clinical pictures that are little suggestive of epilepsy and, therefore, difficult to recognize. Depending on the location and connectivity of the focus, motor symptoms can be rather widespread, synchronously involving groups of muscles, a whole limb, or even an entire body half. These will not go unnoticed. But narrowly localized continuous minimal myocloni, which the patients often fail to report, may be missed, especially when the attention is focused on more obvious seizure types. The twitches may escape inspection and only be revealed by touching the affected area. The same can happen in the rare cases when EPC is the first or only manifestation of epilepsy. Epilepsy essentially is a disorder of seizures, and continuous or quasicontinuous symptoms are an unexpected presentation.

Then, as already noted by Gowers (1881), the sensory cortex and motor cortex in epilepsy typically interact closely, and the motor signs of both individual Jacksonian seizures and EPC are often accompanied by paresthesias or numbness (Janz, 1969). Likewise, somatosensory seizures are frequently followed by motor phenomena (47.4% according to Mauguière & Courjon, 1978). However, this feature is rarely mentioned in the literature, and in this retrospective series we cannot be sure that the symptoms were not sensorimotor more frequently than in seven cases.

Merely somatosensory EPC is even more difficult to recognize and may often be missed. Therefore, the repetitive local paresthesias in the patient of Wolf and Dockweiler (1989), who is included in this study, would not have been diagnosed as EPC without their indispensible and quantitative role as a precondition for the reflex epileptic response, with focal tonic seizures, to touch in the area. Fundamentally, in cases of somatosensory EPC, it would be necessary to monitor electromyographic activity to exclude subtle motor involvement. To establish the true relation of motor, sensorimotor, and somatosensory EPC is another point that needs to be addressed in the prospective investigation.

In other instances the diagnosis can be based upon the development of the clinical condition, such as in one case with a dysontogenetic tumor in the left sulcus frontalis superior, where ictal dysesthesias of the right hand occurred first as part of predominantly motor seizures, then also as independent somatosensory seizures that were gradually replaced by an identical continuous symptomatology. This after unsuccessful treatments with carbamazepine and topiramate was controlled by phenobarbital, whereas brief focal myoclonic seizures continued.

Epileptiform EEG during clinically suspected somatosensory EPC confirmed the diagnosis in the other three cases.

The visual symptoms in our four cases were: continuous whitish photomes at the outer rim of the visual field contralateral to an operated hemangioma, with unrevealing EEG but sometimes evolving into a complex partial seizure via a gradual expansion of more complex photomes over the entire visual field; photomes of lines and circles accompanied by left occipital runs of spikes; flicker in the left visual field which had at first occurred as an isolated focal visual seizure with right occipital epileptiform EEG activity, then as an aura to secondarily generalized tonic–clonic (sGTC) seizures, then in identical perception as a persistent EPC; and a similar development leading up to repetitive 1–2 h episodes of EPC with nonspecific focal ictal EEG abnormalities and a contralateral unspecified occipital MR lesion.

If, therefore, the EEG may confirm the diagnosis, it cannot always be relied upon. In a case of visual EPC reported by Wolf (1980), which started with simple photomes and evolved into complex visual hallucinations accompanied by fragmentary versive seizures of eyes and head, the EEG showed no epileptiform activity but contralateral occipital slow activity and repetitive bouts of ictal nystagmus. At the other end of the spectrum, a focal electrographic status epilepticus persisting over >3 years, with a hypermetabolic focus in the fluorodeoxyglucose–PET (FDG-PET) but without any clinical signs and symptoms, has been described by Sheth and Riggs (1999). One of the problems of EEG diagnostics of EPC is that the technician taking the EEG and interacting directly with the patient may not be aware of this diagnostic possibility and, therefore, may miss important information. The prospective study needs to use a uniform

EEG protocol including standardized tests for the clinical condition.

That only these types of EPC were identified in our case collection does not indicate that others do not exist. They may be rare or have remained undiagnosed due to the factors discussed. Reports exist of auditory (Wolf, 1983), gustatory (Wieser et al., 1985; Seshia & McLachlan, 2005), and olfactory (Wolf, 1982; Manford & Shorvon, 1992) EPC, and Scott and Masland (1953) described a continuous aura consisting of a distortion of proprioception or ''somatognostic illusion'' (Mauguière & Courjon, 1978). The prospective study will attempt to pay special attention to these less well-known possibilities.

Etiology and pathogenesis

Unlike previous series (Thomas et al., 1977; Cockerell et al., 1996; Gurer et al., 2001; Sinha & Satishchandra, 2007) we did not include all etiologies but focused on what remains when the two well-known entities, that is, Rasmussen syndrome and stroke-related EPC, are left out. Minus these, the present series is the largest, and the participation of 19 centers with access to diverse selections of patients provided broad etiopathogenetic variability. However, fewer varieties are represented than reviewed by Schomer (1993) and by Wieser and Chauvel (2008), which indicates still some recruitment bias. This series does not include EPC in patients with impaired consciousness, which made up for 11 of the 32 patients in the study of Thomas et al. (1977), or of subacute sclerosing panencephalitis (SSPE) of which Gurer et al. (2001) had three cases in a series of 21. It is, therefore, hoped that still more groups representing a broader range of catchment join the prospective study.

That EPC is not only observed with strictly localized pathologies but also with systemic, especially toxic and metabolic conditions, has long been known (Singh & Strobos, 1980; Bien & Elger, 2008). EPC in morbus Alpers of which our series contains five examples, was also found in the series of Cockerell et al. (1996). EPC in mitochondrial diseases was reported by Andermann et al. (1986) and Sinha and Satishchandra (2007). EPC in benign rolandic childhood epilepsy was described by Fejerman and Di Blasi (1987), and Colamaria et al. (1991) reported another case presenting as anterior opercular syndrome, like two in our series. The third occurred in an otherwise absolutely unremarkable and fully remitting patient.

The nine patients with motor EPC due to tick-borne Russian spring-summer encephalitis form an interesting subgroup in this study. Seven of them have been published before in Russian language (Mukhin et al., 2006). This etiology of EPC has been discussed since the late 1930s, and was established by Chumakov (1944), who identified the virus in the brains of patients with EPC and transferred the encephalitis to laboratory animals. All our patients belong to the primary type 3, even if the onset was in the acute phase of meningoencephalitis (one case). The others had delayed onset after 1–30 months, two of them following focal seizures in the acute encephalitic phase. At entry, EPC had been going on from 4–13 years. It is tempting to hypothesize that EPC in these cases is the expression of chronic virus inclusion modifying the activity of neurons in the motor cortex.

The rate of unclarified etiologies would probably be lower if optimal investigation protocols would have been used throughout. A standardized imaging protocol will be an indispensible feature of the planned prospective study.

External modification

An interesting feature is the occurrence of reflex epileptic seizure precipitation. This has repeatedly been noted before (Thomas et al., 1977; Obeso et al., 1985; Sinha & Satishchandra, 2007) and was reported in 36.9% of our patients, the trigger usually being real or intended motor activity, proprioception of movement, and touch. Thomas et al. (1977) also reported the counterpart, that is, reduction or disappearance of EPC by rest or sleep but did not mention if both occurred in the same patients as we saw in most cases with EPC due to tick-borne encephalitis. It remains to be seen if this is a specific feature of this etiology or expresses a particular interest of the reporting coauthor (KM) in these mechanisms. The inhibition of EPC by strong innervation has not been described before, whereas spike suppression by movement in sensorimotor cortical epilepsy has recently been demonstrated by Yanagisawa et al. (2009), and precipitation or inhibition by the same stimuli as two related variants of external modification of seizure activity was established as a principle by Guaranha et al. (2009). That the either precipitating or inhibitory effect of touching a trigger zone in one of our patients depended on the timing of the stimulus was described in detail by Wolf and Dockweiler (1989).

Treatment

The study confirms that EPC is a pharmacoresistant condition. However, an at least temporary response to benzodiazepines is not rare, and a number of successful individual schedules have been reported (Table 5). Our earlier observation that topiramate is often successful in EPC with dysontogenetic etiologies (Wolf et al., 2009) is confirmed, and levetiracetam in this larger study appears as another possible treatment of choice. A positive effect of intravenous levetiracetam was recently reported by Eggers et al. (2009).

Disclosure

None of the authors has any conflict of interest to disclose. On behalf of the working group, I confirm that all of us have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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